Congressionally Directed Medical Research Programs
Neurofibromatosis Research Program (NFRP)

Vision

Decrease the impact of neurofibromatosis and Schwannomatosis.

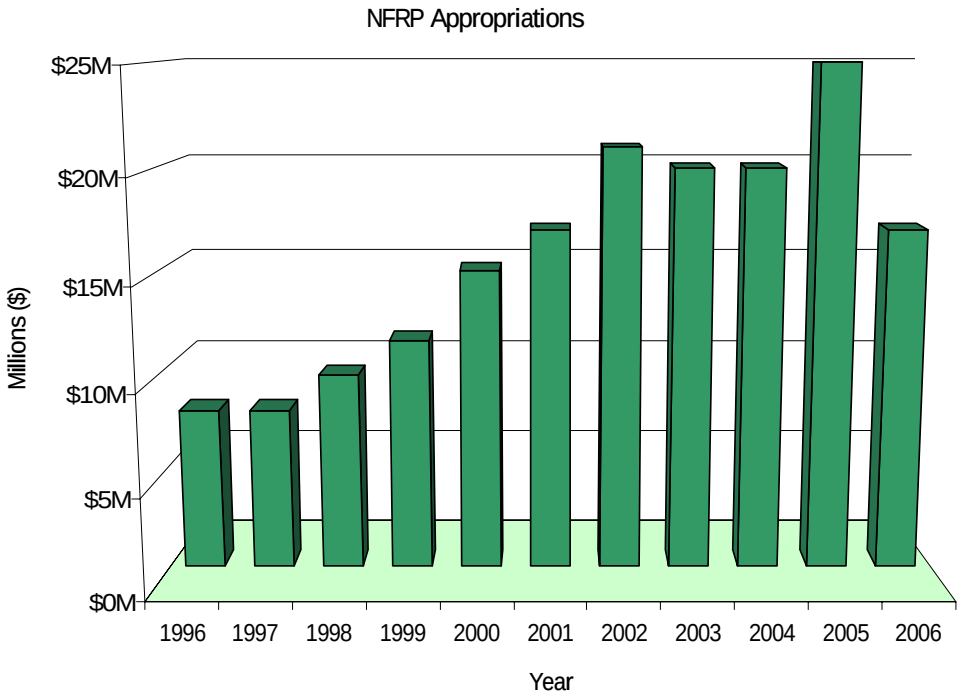
Mission

Promote research directed toward the understanding, diagnosis, and treatment of neurofibromatosis and Schwannomatosis to enhance the quality of life for persons with those diseases.

Introduction to the NFRP

The Office of the Congressionally Directed Medical Research Programs (CDMRP) represents a unique partnership among the public, Congress, and the military. The CDMRP was established within the U.S. Army Medical Research and Materiel Command in 1993, when Congress, in response to grassroots advocacy efforts, tasked the Department of Defense (DOD) with developing and managing an innovative breast cancer research program. Since 1993, the CDMRP has grown to include programs aimed at other major diseases, including prostate cancer and ovarian cancer.

The Neurofibromatosis Research Program (NFRP), established in fiscal year 1996 (FY96) in response to the efforts of neurofibromatosis (NF) advocates, is the second-oldest CDMRP program and a major source of funding for NF1, NF2, and Schwannomatosis investigators worldwide. Funds for the NFRP are added to the DOD budget annually by Congress. Congressional appropriations for the NFRP have increased from $8M in FY96 to $17M in FY06.



Unique Features of the NFRP

Two-Tier Proposal Review Process

The NFRP, like all CDMRP programs, is conducted according to the two-tier review model recommended by the National Academy of Sciences Institute of Medicine. The first tier is a peer review of proposals against established criteria for determining scientific and technical merit. The second tier is a programmatic review, conducted by the Integration Panel (an advisory board of leading scientists, clinicians, and consumer advocates), that compares proposals against each other and recommends submissions for funding based on scientific merit, relative innovation and impact, portfolio balance, and overall program goals. The two-tier model has received high praise from the scientific community, advocacy groups, and Congress.

Consumer Advocate Participation

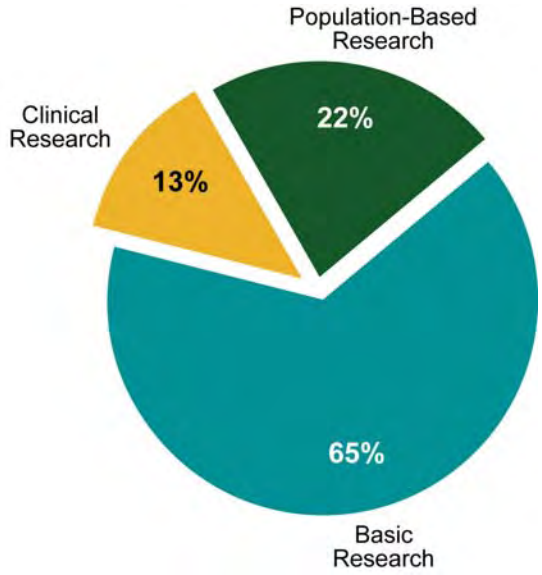
A unique feature of the NFRP is that consumer advocates are active participants in virtually all aspects of program execution. The efforts of the NF and Schwannomatosis consumer advocacy communities have played vital roles in the establishment and continuing growth of the NFRP. Individuals with NF1, NF2, and Schwannomatosis and their family members work in partnership with leading scientists and clinicians to contribute their unique perspectives and ensure that program priorities and funding decisions reflect the concerns and meet the needs of their communities. By serving as liaisons between their constituencies and the scientific community, consumer advocates also enhance awareness of the importance of research and strengthen consumer-scientist relationships.

"By participating as a consumer reviewer for the U.S. Army's CDMRP program I was able to experience first hand a government program at its finest. As the leader of NF research funding worldwide, the NFRP represents to the many faces of NF encouragement, hope and promise for the future. This propitious future is advanced by the collaborative effort of dedicated scientists, clinicians, and consumers working together to support the program's vision of decreasing the impact of NF and Schwannomatosis."

Ms. Suzanne C. Earle, Children's Tumor Foundation
Consumer Advocate and Peer Reviewer, NFRP

Decreasing the Impact of NF and Schwannomatosis through Innovative Research

As a primary source of support for NF and Schwannomatosis research worldwide, the NFRP funds innovative basic, translational, and clinical studies with the potential to improve the detection, diagnosis, treatment, or management of these disorders and the quality of life of affected individuals. The NFRP's flexible management strategy allows for the annual adaptation of the program's vision to meet the changing needs of the field and take advantage of emerging opportunities.



Basic Research

The NFRP's multifaceted approach to supporting basic research includes funding for:

- Established investigators (Investigator-Initiated Research Award [IIRA])
- Recruitment and training of early-career researchers with the potential to revolutionize the field (IIRA Nested Postdoctoral Traineeship Award, New Investigator Award)
- Development and validation of novel tools to advance laboratory-based research (Resource Development Award)
- Innovative, high-risk studies that represent new paradigms or challenge existing paradigms (Concept Award)

Clinical and Translational Research

The NFRP's commitment to funding the best basic research is paralleled by initiatives to accelerate the progression of promising basic science from bench to bedside:

- Natural history studies of the growth of NF1 plexiform neurofibromas and NF2 vestibular schwannomas; these data can aid in the evaluation of therapeutic efficacy in clinical trials (Natural History Study Award)
- Support for preclinical drug development (Therapeutic Development Award)
- Funding for Phase I and Phase II clinical trials (Clinical Trial Award)

The NF Consortium – Building Collaborations to Advance Clinical Care

Overview

The NF Consortium is an unprecedented and groundbreaking initiative that represents great hope and promise for individuals with NF and their families. The Consortium will bring together the nation's leading NF investigators and clinicians to address key questions in NF research and facilitate the rapid execution of clinical trials in ways that cannot be accomplished by individual investigators. The Consortium will initially focus on NF1 but, once established, will have the option of expanding to encompass NF2 and Schwannomatosis studies. By breaking down barriers between research groups and fostering interdisciplinary and multi-institutional alliances, the Consortium has great potential to revolutionize the clinical management and treatment of NF.

FY05 NF Consortium Development Awards

The FY05 NFRP offered two award mechanisms to select participants and fund development of the Consortium:

- NF Consortium Development Operations Center Award:

  Jeannette Lee, Ph.D., University of Alabama at Birmingham; Birmingham, Alabama

- NF Consortium Development Site Award:

  David Gutmann, M.D., Ph.D., Washington University; St. Louis, Missouri
  Mira Irons, M.D., Children's Hospital Boston; Boston, Massachusetts
  Bruce Korf, M.D., Ph.D., University of Alabama at Birmingham; Birmingham, Alabama
  Roger Packer, M.D., Children's National Medical Center; Washington, DC
  Peter Phillips, M.D., Children's Hospital of Philadelphia; Philadelphia, Pennsylvania
  Elizabeth Schorry, M.D., Cincinnati Children's Hospital Medical Center; Cincinnati, Ohio
  James Tonsgard, M.D., University of Chicago; Chicago, Illinois
  David Viskochil, M.D., Ph.D., University of Utah; Salt Lake City, Utah
  Brigitte Widemann, M.D., National Cancer Institute; Bethesda, Maryland

Awardees will collaborate to submit a proposal and clinical protocols to compete for the FY06 NF Consortium Award, which will provide support for the full Consortium for up to 3 years.

NFRP Research Highlights

Notable Advances

- Creation of preclinical mouse models of NF1 and NF2 tumors for studying tumor biology, identifying potential drug targets, and testing novel therapies
- Development of novel therapeutics that suppress NF1 nonsense mutations and allow for the production of full-length NF1 protein
- Development of oncolytic herpes viruses for the treatment of neurofibromas and malignant peripheral nerve sheath tumors
- Characterization of the role of inflammatory cytokines in promoting NF1 tumor growth and invasion – may provide new molecular therapeutic targets

Individual Success Stories

Dr. Roger Packer of Children's National Medical Center, a recipient of a FY01 Clinical Trial Award, is

conducting studies to assess the toxicity and effectiveness of pirfenidone in children with NF1 and progressive plexiform neurofibromas (PNs). PNs, one of the most common tumor types in NF1, can cause disfigurement and severe neurological impairment. There are no effective drugs available for the treatment of PNs, and complete surgical removal of the tumors is often impossible because of their large size. Pirfenidone is a novel oral anti-fibrotic agent that targets growth factors elevated in PNs. Recently completed Phase I safety trials revealed that pirfenidone is well-tolerated in children, and the optimal dose for pediatric patients was identified. Phase II trials examining the effects of the drug on tumor progression and quality of life are underway. Since there are no effective therapies for progressive PNs other than surgery, Dr. Packer's research has the potential to greatly benefit many children with NF1.

Dr. David Gutmann of Washington University, a recipient of a FY02 Investigator-Initiated Research Award,

has identified mechanisms underlying the limited effectiveness of farnesyltransferase inhibitors (FTIs) in treating NF1-associated tumors. *NF1* inactivation is associated with increased activation of growth-stimulating Ras proteins, suggesting that FTIs and other Ras inhibitors may block NF1-associated tumor growth. However, preliminary human studies with FTIs have been disappointing. Dr. Gutmann used primary brain cell cultures (astrocytes) from mice lacking *Nf1* gene expression ($Nf1^{+/-}$ mice) to examine the roles of the three types (isoforms) of Ras proteins in astrocyte cell growth. *Nf1* loss in astrocytes, which form tumors known as gliomas, increased the activation of K-Ras but not the other Ras isoforms. Activation of K-Ras in normal astrocytes mimicked the effects of *Nf1* loss on cell growth and migration, whereas inhibition of K-Ras reversed the biological abnormalities observed in astrocytes lacking *Nf1* expression. Additionally, $Nf1^{+/-}$ mice with K-Ras, but not H-Ras, activation in astrocytes developed optic pathway gliomas. These results suggest that K-Ras is the primary target for neurofibromin in astrocytes and that increased activation of K-Ras plays a critical role in the formation of NF1-associated gliomas. Importantly, FTIs are known to have minimal effects on K-Ras function, indicating that drugs specifically targeting K-Ras or proteins activated by K-Ras may be more effective than FTIs for the treatment of NF1-associated tumors.

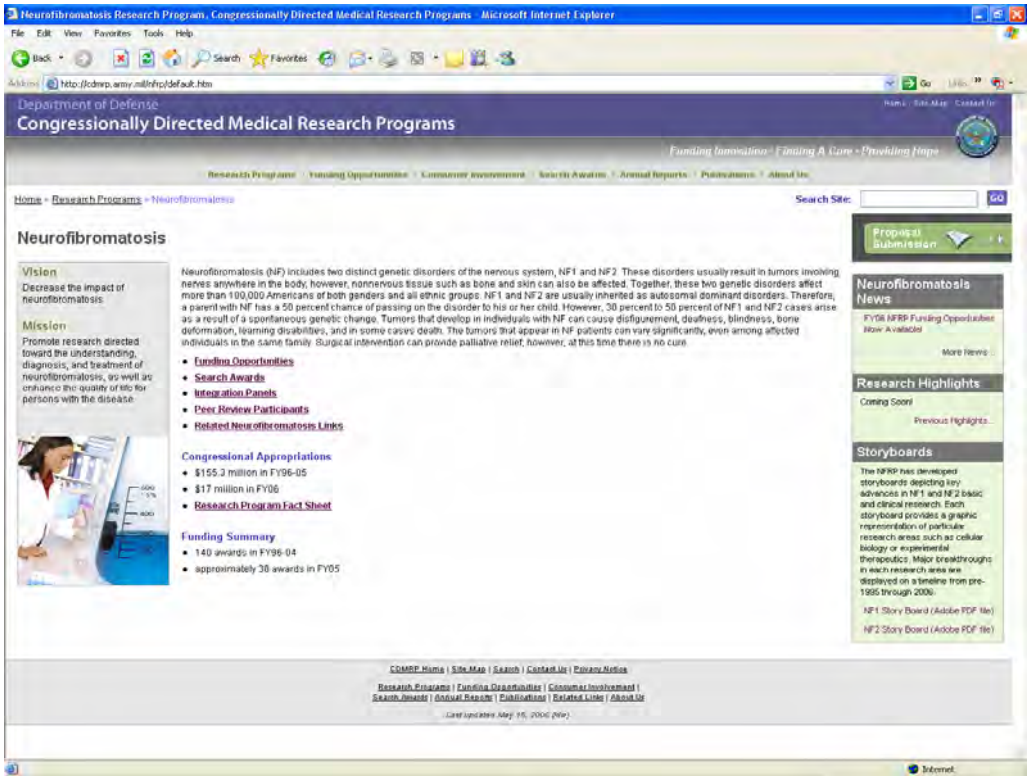
Dr. Jan Dumanski of the University of Alabama at Birmingham (formerly at Uppsala University), a leader in

the field of array-based comparative genomic hybridization (CGH), a cutting-edge genetic analysis technology, received Investigator-Initiated Research Award grants in FY99 and FY03 to elucidate the molecular and genetic mechanisms of clinical variability in NF2, which differs widely in symptoms and severity among affected individuals. His group found no correlations between specific deletions in the NF2 gene (also called merlin or schwannomin) and disease severity, suggesting that the observed variability may be caused by other genes, known as "modifier genes," that affect NF2 symptom development. They hypothesize that the gene responsible for the development of Schwannomatosis, which is closely related to NF2, may be an NF2 modifier gene. A candidate Schwannomatosis gene has been identified on the same chromosome as merlin, and further analysis of this gene is in progress. Other ongoing projects include (1) the identification of genes contributing to the development of NF2 ependymomas, meningiomas, and astrocytomas; (2) analysis of regulatory elements in the NF2 gene, which may control the timing, location, and amount of merlin protein produced; and (3) improvement of array-CGH methodology for the diagnosis of NF2. Dr. Dumanski's research will help improve

understanding of the molecular mechanisms underlying NF2 and Schwannomatosis and provide a foundation for the development of improved therapies for these disorders.

Dr. Nancy Ratner and her colleague Dr. Shyra Miller of the Cincinnati Children's Hospital Medical Center have made great strides in elucidating the molecular mechanisms underlying the development of NF1 malignant peripheral nerve sheath tumors (MPNSTs). These tumors, which are believed to arise from abnormal Schwann cells in benign plexiform neurofibromas, are a major cause of mortality of NF1. The team's latest work, supported primarily by a FY00 Idea Award and a FY03 Investigator-Initiated Research Award, examined the genetic differences between NF1-associated malignant tumor cells and their normal human Schwann cell counterparts using state-of-the-art oligonucleotide microarray chips. Although the rates of proliferation and gene expression profiles in the malignant cell lines were somewhat variable, the team was able to identify and validate a 159-gene signature that distinguished MPNST cells from normal Schwann cells. Many of these genes have been implicated in other cancers, suggesting that therapeutics developed for other types of tumors may be useful for the treatment of MPNSTs. Importantly, TWIST1, which is involved in tumor migration, invasion, and drug resistance, was overexpressed in all of the malignant cell lines tested and was found to promote migration. This research has great potential to identify new diagnostic biomarkers and drug targets to combat malignancies associated with NF1.

http://cdmrp.army.mil/nfrp



http://cdmrp.army.mil